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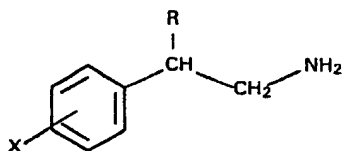
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① Irreversible dopamine-Beta-hydroxylase inhibitors.

② Substituted β -ethenyl and β -ethynyl benzeneethanamine compounds of structure (I)



in which X is hydrogen or hydroxy; and R is ethenyl or ethynyl; are potent, irreversible inhibitors of mammalian dopamine- β -hydroxylase. Included are pharmaceutical compositions and methods for using these compounds to inhibit DH, and processes and intermediates used in preparing active compounds.

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TITLEIRREVERSIBLE DOPAMINE- β -HYDROXYLASE INHIBITORSFIELD OF THE INVENTION

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This invention relates to novel compounds that irreversibly inhibit dopamine- β -hydroxylase, and novel pharmaceutical compositions, and methods for inhibiting dopamine- β -hydroxylase.

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BACKGROUND OF THE INVENTION

In the catecholamine biosynthetic pathway, tyrosine is converted in three steps to norepinephrine (NE). Intermediates are dihydroxyphenylalanine (DOPA) and dopamine (DA). Dopamine is hydroxylated to norepinephrine by dopamine- β -hydroxylase (DBH) in the presence of oxygen and ascorbic acid.

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Inhibition of catecholamine activity decreases blood pressure. Weinshilboum, Mayo Clin. Proc. 55, 39 (1980), reviews compounds that inhibit catecholamine activity by acting upon adrenergic receptors. Alternatively, the catecholamine biosynthetic pathway can be suppressed at any of the three steps, resulting in reduced NE levels. In addition to producing an antihypertensive effect, inhibitors of NE synthesis are

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1 active as diuretics, natriuretics, cardiotonics, and
vasodilators. Inhibition of DBH activity can have the
added advantage of increasing DA levels, which as reported
by Ehrreich et al., "New Antihypertensive Drugs," Spectrum
5 Publishing, 1976, pp. 409-432, has selective vasodilator
activity at certain concentrations.

DBH inhibitors also have been shown to reduce or
prevent formation of gastric ulcers in rats by Hidaka et
al., "Catecholamine and Stress," edit. by Usdin et al.,
10 Pergamon Press, Oxford, 1976, pp. 159-165 and by Osumi et
al., Japan J. Pharmacol. 23, 904 (1973).

A number of reversible DBH inhibitors are known.
These generally are divided into two classes, namely, metal
chelating agents, which bind copper in the enzyme, and
15 phenethylamine analogues. Rosenberg et al., "Essays in
Neurochemistry and Neuropharmacology," Vol. 4, edit. by
Youdim et al., John Wiley & Sons, 1980, pp. 179-192, and
Goldstein, Pharmacol. Rev. 18(1), 77 (1966), review DBH
inhibitors. The former report that many potent DBH
20 inhibitors have a hydrophobic side chain of size comparable
to the aromatic ring of DA, leading the authors to suggest
that incorporation of a terminal hydroxyl group on a 4- to
6- carbon side chain on a phenethylamine analogue may
yield potent inhibitors.

25 Known reversible DBH inhibitors include:

(a) 5-alkylpicolinic acids [See, Suda et al.,
Chem. Pharm. Bull 17, 2377 (1969); Umezawa et al.,
Biochem. Pharmacol. 19, 35 (1969); Hidaka et al., Mol.
Pharmacol 9, 172 (1973); Miyano et al., Chem. Pharm. Bull.
30 26, 2328 (1978); Miyano et al., Heterocycles 14, 755
(1980); Claxton et al., Eur. J. Pharmacol. 37, 179 (1976)];

(b) BRL 8242 [See, Claxton et al., Eur. J.
Pharmacol. 37, 179 (1976)];

1 (c) 1-alkylimidazole-2-thiols [See, Hanlon et al., Life Sci. 12, 417 (1973); Fuller et al., Adv. Enzyme Regul. 15, 267 (1976)];

(d) substituted thioureas [See, Johnson et al.,
5 J. Pharmacol. Exp. Ther. 168, 229 (1969)]; and

(e) benzyloxyamine and benzylhydrazine [See,
Creveling et al., Biochim. Biophys. Acta 64, 125 (1962);
Creveling et al., Biochim. Biophys. Acta 8, 215 (1962);
Van Der Schoot et al., J. Pharmacol. Exp. Ther. 141, 74
10 (1963); Bloom, Ann. N.Y. Acad. Sci. 107, 878 (1963)].

Each of the above compounds except benzyloxyamine and benzylhydrazine apparently owes its inhibitory effect to metal chelating properties. Alkyl derivatives of imidazole-2-thiol are more potent, presumably due to non-specific interaction of the alkyl substituent with the
15 enzyme. Benzyloxyamine and benzylhydrazine are phenethylamine analogues which apparently act as competitive inhibitors.

In addition to the above compounds, Runti et al.,
20 Il Farmaco Ed. Sci. 36, 260 (1980), report that other fusaric acid derivatives and analogues inhibit DBH. These include phenylpicolinic acid, which has twice the inhibitory activity of fusaric acid, and 5-(4-chlorobutyl)picolinic acid, and others such as substituted amides of
25 fusaric acid and acids and amides of 5-butyroylpicolinic acid, 5-aminopicolinic acid and 5-hydrazinopicolinic acid, and derivatives thereof.

Hidaka et al., Molecular Pharmacology, 9, 172-177 (1972) report that 5-(3,4-dibromobutyl)picolinic acid and
30 5-(dimethyldithiocarbamoyl)methylpicolinic acid are DBH inhibitors.

Bupicomide, 5-(n-butyl)picolinamine, is reported by Ehrreich et al., "New Antihypertensive Drugs", Spectrum Publications, 1976, pg. 409-432, to be a DBH inhibitor that
35 possesses the ability to lower blood pressure.

1 In European Patent Application No. 125,033 a
series of 1-phenyl and 1-phenylalkylimidazole compounds
having a mercapto or alkylthio group in the 2-position are
disclosed. These compounds are described as having DBH
5 inhibiting activity.

United States Patent No. 4,532,331 describes
various 1-benzyl-2-aminomethylimidazole derivatives that
inhibit DBH activity and includes pharmaceutical
compositions containing these derivatives and methods of
10 using these derivatives to inhibit DBH activity.

United States Patent No. 4,487,761 describes
several methylpyridine derivatives isolated from the
fermentation broth of a strain of Streptovercillium.
These compounds inhibit DBH activity.

15 Friedman et al., Psychosomatic Med. 40, 107
(1978), report that patients treated with alpha-methyl-
DOPA, guanethidine, and reserpine, but not propranolol and
diuretics, have lowered DBH levels, although the
significance of the observation is uncertain.

20 Non-specific, often toxic effects of known DBH
inhibitors have obviated clinical use of these compounds.
Fusaric acid, for example, is hepatotoxic. See, for
example, Teresawa et al., Japan. Cir. J. 35, 339 (1971)
and references cited therein. Presumably, the picolinic
25 acid structure interacts with a number of metalloproteins
and enzymes non-specifically to produce the observed side
effects.

SUMMARY OF THE INVENTION

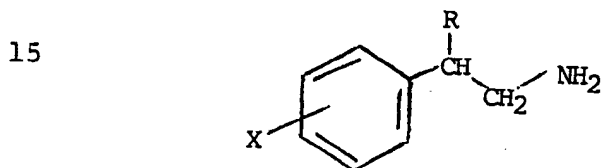
30 The present invention resides in the discovery
that DBH is inhibited by substituted β -ethynyl and
 β -ethenyl benzeneethanamine compounds and that the DBH
inhibition produced by these compounds is irreversible.
These compounds are potent and produce prolonged DBH
35 inhibition.

1 Presently preferred compounds of the invention
include:

3 β -ethynylbenzeneethanamine,
5 β -ethynyl-3-hydroxybenzeneethanamine,
 β -ethynyl-4-hydroxybenzeneethanamine,
 β -ethenylbenzeneethanamine,
 β -ethenyl-3-hydroxybenzeneethanamine, and
 β -ethenyl-4-hydroxybenzeneethanamine.

10 DETAILED DESCRIPTION OF THE INVENTION

The presently invented compounds that
irreversibly inhibit DBH have the following formula:



(I)

20 in which:

X is hydrogen or hydroxy; and
R is ethynyl or ethenyl;

or a pharmaceutically acceptable salt or hydrate thereof.

25 Compounds of Formula I are prepared from
substituted phenylmethylenes by processes such as
shown in Scheme I below. In Scheme I, X^1 is hydrogen or
para- C_{1-4} alkoxybenzyloxy, R^2 is 1,3-propanedioic acid
di- C_{1-4} alkyl ester, preferably diethyl ester, or
30 2,2-dimethyl-1,3-dioxane-4,6-dione, and X is as described
in Formula I, above.

Scheme I illustrates reaction of a substituted
phenylmethylenes (A) with a tri- C_{1-4} alkylsilylacetylene,
Grignard, preferably trimethylsilylacetylene, followed by
35 addition of a strong acid such as hydrochloric acid, to

1 prepare substituted phenyl(trimethylsilylethynyl)methyl-
propanedioic acid diethyl esters (B) or substituted
2,2-dimethyl-5-phenyl(trimethylsilylethynylmethyl)-1,3-
dioxane-4,6-diones (C).

5 Substituted β -ethynylbenzenepropanoic acid
compounds (D) then are prepared by heating at about 80 to
120°C formula (B) compounds with a strong base such as an
alkali metal hydroxide, for example sodium hydroxide,
acidifying this reaction mixture with strong acid, such as
10 hydrochloric acid, to obtain the diacid, followed by
heating at about 80 to 120°C the diacid with aqueous
organic base such as triethylamine, aminopyridine, or,
preferably, pyridine.

Formula (D) compounds also are prepared by
15 heating at about 80 to 120°C a mixture of a formula (C)
compound with an aqueous organic base such as
triethylamine, aminopyridine, or, preferably, pyridine,
then heating the mixture at about 40-60°C with potassium
fluoride in a dipolar, aprotic solvent such as
20 dimethylformamide, thereby producing a salt, and then
acidifying the salt by addition of strong acid such as
hydrochloric acid.

The substituted β -ethynylbenzenepropanoic acid
compounds (D) thus formed next are heated at about 80 to
25 120°C with diphenylphosphorylazide, an organic base,
preferably triethylamine, and a 4-C₁₋₄alkoxybenzyl
alcohol, such as 4-methoxybenzyl alcohol (PMBOH), to
prepare substituted 2-(ethynyl-2-phenylethyl)carbamic
acid, 4-methoxyphenylmethyl esters (E).

30 To prepare Formula I compounds having a β -ethynyl
group (F), formula (E) compounds are deprotected by
addition of a saturated ethereal hydrochloride solution.
Formula (I) compounds having a β -ethenyl group (H) are
formed by hydrogenation of formula (E) compounds over
35 Lindlar catalyst (palladium on calcium carbonate poisoned

1 with lead) available from Aldrich Chemical Company to
produce formula (G) compounds followed by deprotection of
the formula (G) compounds by addition of a saturated
ethereal hydrochloride solution.

5 Formula (I) compounds in which X is hydrogen or
hydroxy at the 2 or 3 position can be prepared from
formula (A) compounds wherein R^2 is a 1,3-propanedioic
acid diC₁₋₄ alkyl ester or 2,2-dimethyl-1,3-dioxane-
4,6-dione. According to the reactions of Scheme (I),
10 however, Formula (I) compounds wherein X is 4-hydroxy must
be formed from formula (A) compounds wherein R^2 is
2,2-dimethyl-1,3-dioxane-4,6-dione.

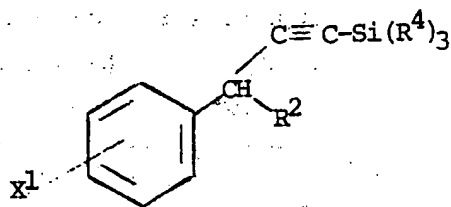
Starting formula (A) compounds that are
phenylmethylenepropanedioic acid diC₁₋₄alkyl esters (X
15 is H) are available and can be prepared by known
procedures. Formula (A) compounds having an para-C₁₋₄
alkoxybenzyloxy group are prepared from corresponding
hydroxy compounds by alkylation with a suitable
alkoxybenzyl halide, such as methoxybenzyl chloride, by
20 known processes. The corresponding hydroxy compounds are
available and can be prepared by known techniques.

Formula (A) compounds that are 2,2-dimethyl-1,3-
dioxane-4,6-diones are prepared from corresponding
alkoxybenzyloxybenzaldehydes by reaction with Meldrum's
25 acid (2,2-dimethyl-1,3-dioxane-4,6-dione) according to
known procedures. For example, a methoxybenzyloxybenz-
aldehyde in an organic solvent such as toluene is reacted
with Meldrum's acid in the presence of glacial acetic acid
and piperidine to yield methoxybenzyloxybenzaldehyde-1,3-
30 dioxane-4,6-dione compounds of formula (A).

The present invention includes compounds of the
following Formulae II, III, and IV that are useful in
preparing Formula (I) compounds of the invention:

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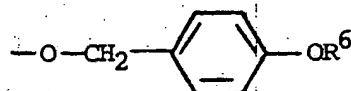


(II)

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in which:

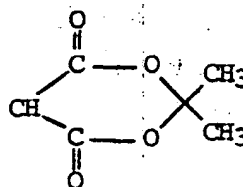
X^1 is H or



R^6 is C_{1-4} alkyl;

R^2 is $CH(CO_2R^7)_2$ or

15

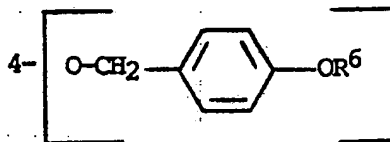


R^7 is C_{1-4} alkyl; and

R^4 is C_{1-4} alkyl;

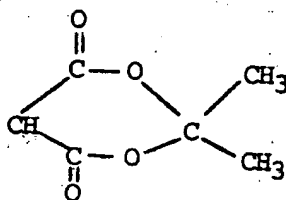
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provided that when X^1 is

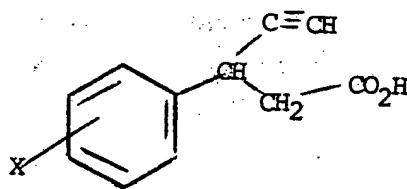


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R^2 is




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(III)

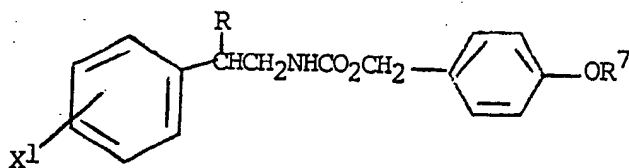
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1 in which:

X^1 is H or $-O-CH_2-$  $-OR^6$
 R^6 is C_{1-4} alkyl.

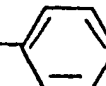
and

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10

in which

X^1 is H or $-O-CH_2-$  $-OR^6$;

R^6 and R^7 are C_{1-4} alkyl; and

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R is $-C\equiv CH$ or $-CH=CH_2$.

Also included in the invention are novel methods of synthesizing compounds of Formulae (II), (III), and (IV) as depicted in Scheme I above and described in the examples that follow.

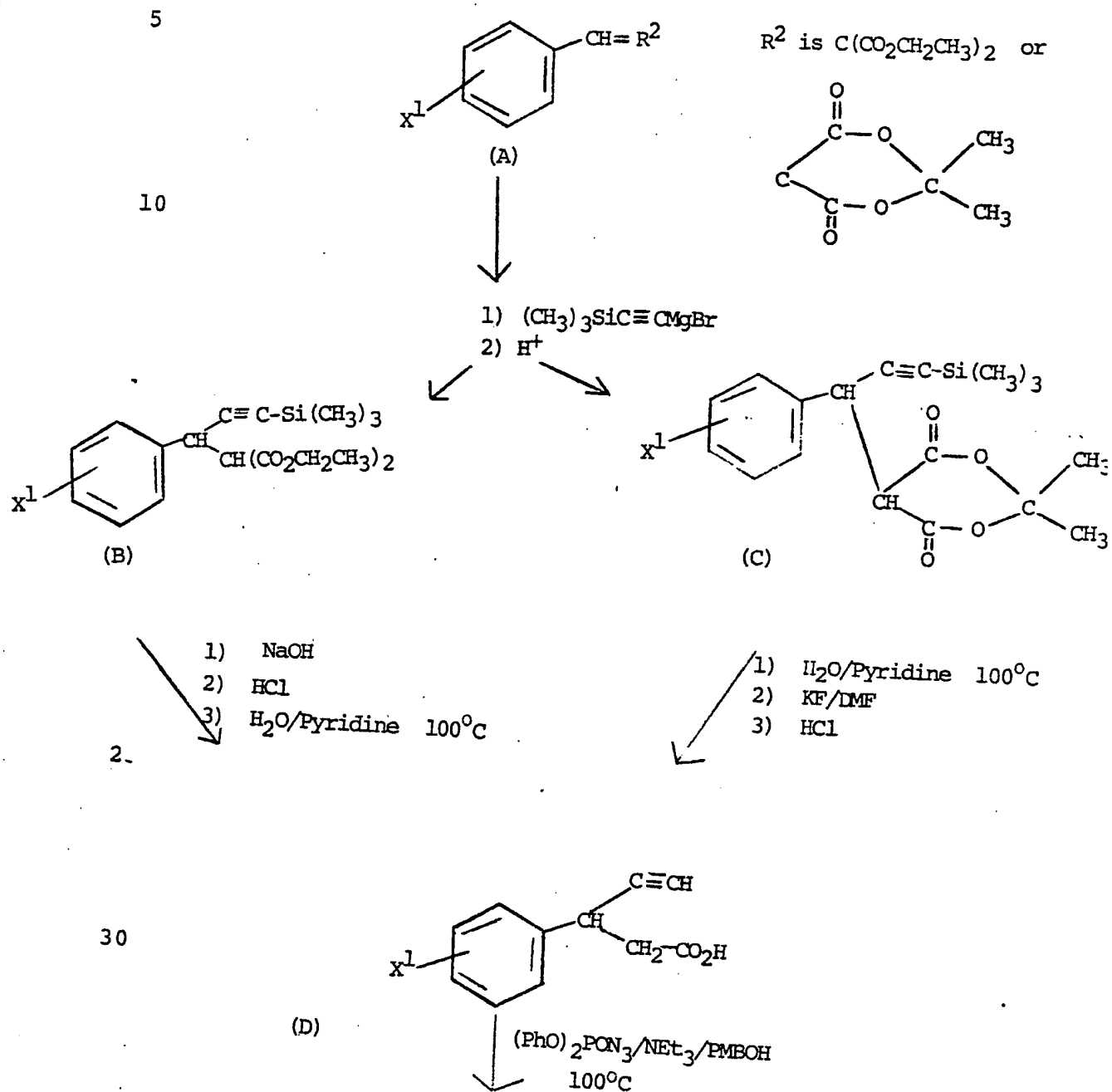
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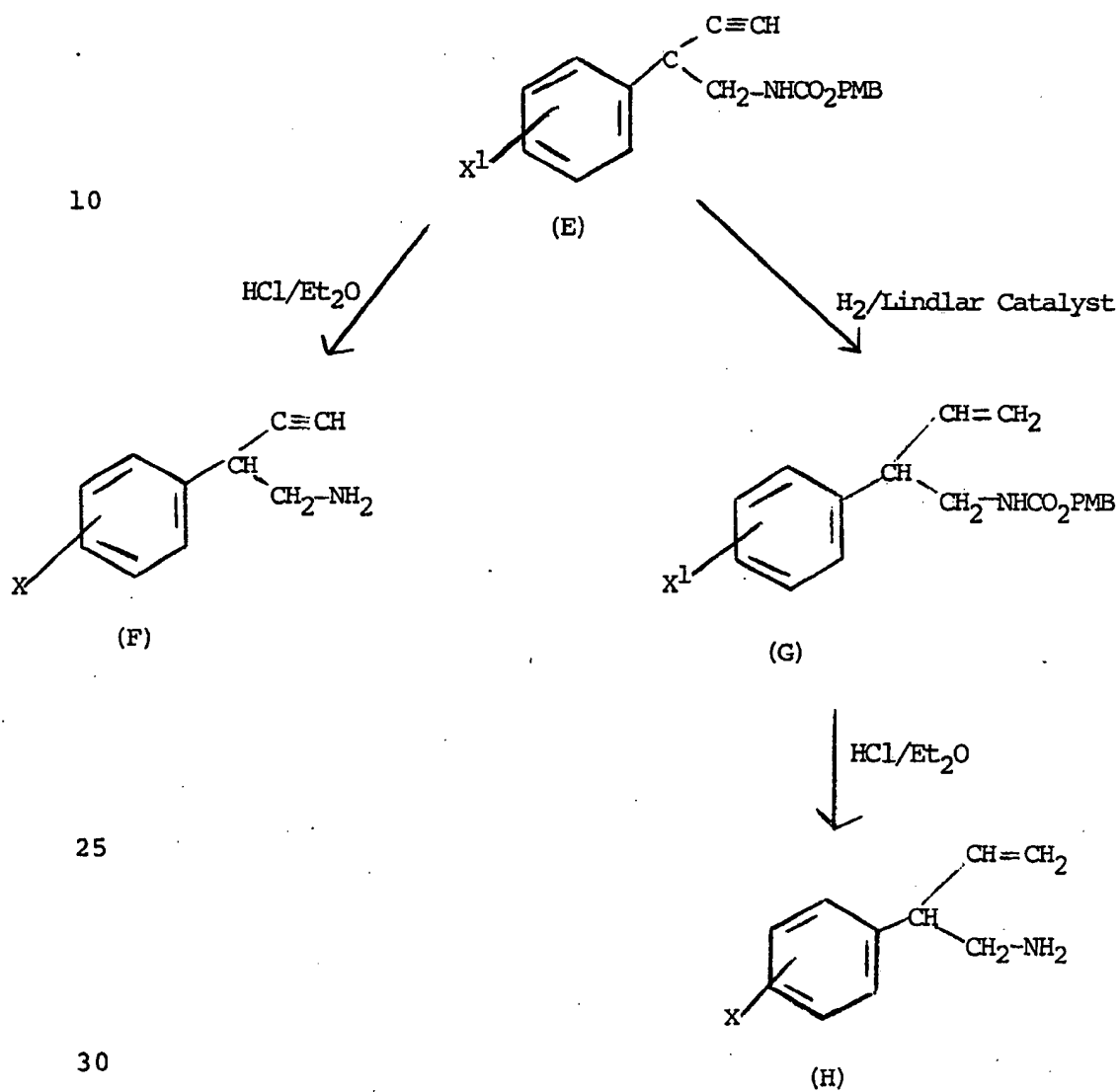
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Scheme I



Scheme I (Continued)



1 The pharmaceutically acceptable acid addition
salts of the Formula (I) compounds are formed with strong
or moderately strong organic or inorganic acids by methods
known in the art. For example, the base is reacted with
5 an inorganic or organic acid in an aqueous miscible
solvent such as ethanol with isolation of the salt by
removing the solvent or in an aqueous immiscible solvent
when the acid is soluble therein, such as ethyl ether or
chloroform, with the desired salt separating directly or
10 isolated by removing the solvent. Exemplary of the salts
which are included in this invention are maleate,
fumarate, lactate, oxalate, methanesulfonate,
ethanesulfonate, benzenesulfonate, tartrate, citrate,
hydrochloride, hydrobromide, sulfate, phosphate and
15 nitrate salts.

 Presently invented, also are methods of producing
DBH inhibition in mammals, including humans, by
administering an effective amount of a β -ethynyl or
 β -ethenyl benzeneethamine compound of Formula (I).

20 In vitro enzyme inhibition kinetic studies
demonstrate that the compounds useful in the methods of
the invention are potent DBH inhibitors. DBH activity was
assayed by a standard procedure for measuring the
conversion of tyramine to octopamine in the presence of
25 DBH. J.J. Pisano, et al., Biochim. Biophys. Acta, 43,
566-68 (1960). Octopamine was assayed following sodium
periodate oxidation to p-hydroxybenzaldehyde by measuring
spectrophotometric absorbance at 330 nm.

 To measure DBH inhibition, the enzyme was
30 incubated for up to 50 minutes with 10, 20, 40, or 80 M
concentrations of β -ethynyl-4-hydroxybenzeneethanamine.
This compound of the invention produced concentration-
dependent DBH inhibition. Additionally, the enzyme
inhibition was time-dependent which indicates that
35 compounds of the invention are irreversible DBH inhibitors.

1 In vivo studies demonstrate that compounds useful
in the methods of the invention effectively reduce blood
pressure. Spontaneously hypertensive rats were dosed with
a suspension or solution of β -ethynylbenzeneethanamine
5 methane sulfonate at a dose of 100 mg/kg
intraperitoneally, and mean arterial blood pressure was
monitored for 260 minutes using indwelling cannulae
positioned in the tail arteries. Approximate twenty
percent reductions in blood pressure were observed twenty
10 to forty minutes following administration of this
compound. At 260 minutes after administration of this
compound, blood pressure remained reduced by approximately
twenty percent when compared to vehicle-treated controls.

Blood pressure also was monitored in spontaneously
15 hypertensive rats given 100 mg/kg intraperitoneally
 β -ethynyl-3-hydroxybenzeneethanamine hydrochloride. Forty
minutes following compound administration approximate
thirty percent blood pressure reductions were observed.
At 260 minutes after compound administration blood
20 pressure remained decreased approximately ten percent.

The compounds useful in the methods of this
invention can be incorporated into convenient dosage forms
such as capsules, tablets or injectable preparations.
Solid or liquid pharmaceutical carriers can be employed.
25 Solid carriers include, starch, lactose, calcium sulfate
dihydrate, terra alba, sucrose, talc, gelatin, agar,
pectin, acacia, magnesium stearate, and stearic acid.
Liquid carriers include syrup, peanut oil, olive oil,
saline, and water. Similarly, the carrier or diluent may
30 include any prolonged release material, such as glyceryl
monostearate or glyceryl distearate, alone or with a wax.
The amount of solid carrier varies widely but, preferably,
will be from about 25 mg to about 1 g per dosage unit.
When a liquid carrier is used, the preparation will be in
35 the form of a syrup, emulsion, soft gelatin capsule,

1 sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating and compressing, 5 when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the present compounds in a pharmaceutical dosage unit will be an efficacious, 10 nontoxic quantity selected from the range of 0.1-1,000 mg/kg of active compound, preferably 10-100 mg/kg. The selected dose is administered orally, rectally, or by injection from one to six times daily, or continuously by 15 infusion to a human patient in need of treatment. Parenteral administration, which uses lower dosages, is preferred. Oral administration, at higher dosages, however, also can be used when safe and convenient for the patient.

20 The following examples are illustrative of preparation of β -ethynyl and β -ethenyl benzeneethanamine compounds and pharmaceutical compositions including these compounds. The examples are not intended to limit the scope of the invention as defined hereinabove and as 25 claimed below. All temperatures and melting points (mp) are given in degrees Celsius ($^{\circ}\text{C}$).

EXAMPLE 1

β -Ethynylbenzeneethanamine

30 A mixture of Mg turnings (1.4 g, 0.058 g-atom) and THF (75 ml) was stirred under argon while a solution bromoethane (7.3 g, 0.067 mol) in THF (10 ml) was added. Iodomethane (0.05 ml) was added to initiate the reaction and after the dissolution of the Mg turnings ceased (30-40 35 min), a solution of trimethylsilylacetylene (6.34 g, 0.065

1 mol) in THF (20 ml) was added, and the resulting solution
 was stirred at ambient temperature for one hour. A
 solution of phenylmethylenepropanedioic acid diethyl ester
 (0.029 mol) in THF (100 ml) was added and the resulting
 5 solution was stirred until the phenylmethylenepropanedioic
 acid diethyl ester had completely reacted as judged by
 TLC. The reaction mixture was poured into saturated
 aqueous ammonium chloride and the product was extracted
 with ethyl acetate. The organic extracts were washed with
 10 water, and dried to afford a 60% yield of phenyl-
 (trimethylsilylethynyl)methylpropanedioic acid diethyl
 ester.

A solution of phenyl(trimethylsilylethynyl)methyl
 propanedioic acid diethyl ester (0.014 mol) in ethanol
 15 (45 ml) was stirred during the addition of a solution of
 sodium hydroxide (1.68 g, 0.042 mol) in water (105 ml) and
 then heated at 100°C until a clear solution resulted. The
 aqueous layer was cooled and acidified to pH 2 with 12N
 HCl, and the product was extracted with ethyl acetate.
 20 The ethyl acetate extracts were washed with water, dried,
 and concentrated to yield β -ethynylbenzenepropanoic acid.
 The crude acid was heated at 170°C under argon until the
 evolution of carbon dioxide ceased. The cooled melt was
 dissolved in ethyl acetate (50 ml) and the resulting
 25 solution was extracted with 10% aqueous sodium hydroxide
 solution. The ethyl acetate extracts were washed with
 water, dried, treated with activated carbon to yield (76%)
 β -ethynylbenzenepropanoic acid as a crystalline solid: mp
 83-86°C.

30 (2-Ethynyl-2-phenylethyl)carbamic acid,
 4-methoxyphenylmethyl ester was prepared in 52% yield by
 heating at 100°C for eight hours β -ethynylbenzene-
 propanoic acid with diphenylphosphoryl azide (1 eq.),
 triethylamine (1 eq.), and 4-methoxybenzyl alcohol (1 eq.).
 35 The reaction mixture was cooled, concentrated, and

- 1 partitioned between water and ethyl acetate. The ethyl acetate was concentrated to give a solid residue: mp. 88-89°C.
- 5 (2-Ethynyl-2-phenylethyl)carbamic acid, 4-methoxyphenylmethyl ester then was deprotected by the following procedure. A solution of the carbamate (1 gm) in 1:1 ethyl acetate:ether (60 ml) was stirred during the addition of a saturated ethereal HCl solution (20 ml) and stirring was continued until the solution became cloudy.
- 10 The solution was allowed to stand at ambient temperature until crystallization was complete. Recrystallization from methanol:ethyl acetate yielded (63%) β -ethynylbenzeneethanamine hydrochloride: mp. 206-208°C.

15

EXAMPLE 2

β -Ethynyl-3-Hydroxybenzeneethanamine

- (3-Hydroxyphenylmethylene)propanedioic acid diethyl ester was alkylated with 4-methoxybenzyl chloride by treatment with sodium hydride in DMF. The crude
- 20 product was purified by flash chromatography using 3:1 hexane:ethyl acetate as eluant to yield (85%) [3-(4-methoxyphenylmethoxy)phenylmethylene]propanedioic acid, diethyl ester.
- The reaction of [3-(4-methoxyphenylmethoxy)phenylmethylene] propanedioic acid diethyl ester with trimethylsilylacetylene magnesium bromide prepared as in Example 1
- 25 yielded 47% of [3-(4-methoxyphenylmethoxy)phenyl]-3-(trimethylsilylethynyl)methylpropanedioic acid diethyl ester as an oil after substantial purification by flash
- 30 chromatography using 5:1 hexane:ethyl acetate.
- A solution of the propanedioic acid diethyl ester (6.77 g, 0.014 mol), prepared as above, in ethanol (45 ml) was stirred during the addition of a solution of sodium hydroxide (1.68 g, 0.042 mol) in water (105 ml) and then
- 35 heated at 100°C until a clear solution resulted. The

1 solution was stirred an additional 1 hr at ambient
temperature and then diluted with water and extracted with
ethyl acetate. The aqueous layer was cooled and acidified
to pH 2 with 12N HCl, and the product was extracted with
5 ethyl acetate. The ethyl acetate extracts were washed
with water, dried, and concentrated to yield 3.95 g (66%)
of [3-(4-methoxyphenylmethoxy)phenyl](trimethylsilyl-
ethynyl)methylpropanedioic acid. A solution of crude
diacid (5.49 g, 0.013 mol) in 3:1 pyridine:water (50 ml)
10 was heated to 100°C for 1 hr. The reaction mixture was
cooled, carefully acidified to pH 2 with 12N HCl, and
extracted with ethyl acetate. The organic extracts were
dried and concentrated and the residue was dissolved in a
minimum amount of ethanol containing sodium hydroxide
15 (0.52 g, 0.013 mol). The ethanol solution was diluted
with water (100 ml) and extracted with ethyl acetate. The
aqueous phase was cooled and acidified to pH 2 with 12N
HCl and the product was extracted with ethyl acetate. The
ethyl acetate extracts were washed with water, dried,
20 treated with activated carbon, and concentrated to yield
3.32 g (65%) of β -(ethynyl-3-(4-methoxyphenylmethoxy)-
benzenepropanoic acid: mp. 141-142°C.

The reaction of the benzenepropanoic acid
prepared above in a procedure analogous to that used in
25 Example 1 yielded [2-ethynyl-2-[3-(4-methoxyphenylmethoxy)-
phenyl]ethyl]carbamic acid 4-methoxyphenylmethyl ester
(35%): mp. 64-67°C.

A solution of [β -ethynyl-2-[3-(4-methoxyphenyl-
methoxy)phenyl]ethyl]carbamic acid, 4-methoxyphenylmethyl
30 ester (0.90 g, 1.9 mmol) in ethyl acetate (20 ml) was
treated with saturated ethereal HCl solution (2 ml) and
stirred at ambient temperature until the reaction was
complete as judged by TLC. Ether was added, the
precipitate was filtered and dissolved in ethanol (3 ml)
35 and this solution was added to a suspension of silver

1 acetate (0.315 g., 1.9 mmol) in ethanol (4 ml) and the
mixture was stirred for 3 minutes and filtered. The
filtrate was mixed with a solution of oxalic acid (0.171
g, 1.9 mmol) and the resulting solution was concentrated
5 under reduced pressure. The residue was triturated with
acetonitrile and recrystallized from methanol--
acetonitrile to yield 0.117 g (25%) of β -ethynyl-3-
hydroxybenzeneethanamine, oxalate: mp. 176-178°C

10 A solution of the carbamate prepared above was
deprotected using ethereal hydrochloride as in Example 1
to yield β -ethynylbenzeneethanamine hydrochloride (63%):
mp. 206-208°C.

EXAMPLE 3

15 β -Ethynyl-4-Hydroxybenzeneethanamine Hydrochloride

A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione
(14.4 g, 0.10 mol) and 4-(4-methoxybenzyloxy)benzaldehyde
(24.2 g, 0.10 mol) in toluene (100 ml) was treated with
glacial acetic acid (2 ml) and piperidine (1 ml). The
20 solution was stirred and heated at reflux until Dean-Stark
removal of water was complete. The reaction mixture was
cooled and the resulting solid orange product was filtered
and washed with cold toluene to yield 24.9 g (68%) of 2,2-
dimethyl-5-[4-(4-methoxyphenylmethoxy)phenylmethylene]-1,3-
25 dioxane-4,6-dione: mp. 155-157°C.

A solution of the 1,3-dioxane-4,6-dione (10.7 g,
0.029 mol), prepared above, in THF (100 ml) was added to a
solution of trimethylsilylacetylene magnesium bromide
prepared as in Example 1, and the resulting solution was
30 stirred until the reaction was complete as judged by TLC.
The reaction mixture was poured into saturated aqueous
ammonium chloride and the product was extracted with ethyl
acetate. The organic extracts were washed with water,
dried, and concentrated to yield 13.2 g (100%) of
35 2,2-dimethyl-5[4-(4-methoxyphenylmethoxy)phenyl]

- 1 (trimethylsilylethynylmethyl]-1,3-dioxane-4,6-dione:
mp. 132-135°C.

A solution of the trimethylsilylethynylmethyl-1,3-dioxane-4,6-dione (14.2 g, 0.131 mol), prepared as above,
5 in 3:1 pyridine:water (120 ml) was heated at 100°C for 4 hr then cooled in ice. The cold solution was carefully acidified to pH 2 with 12N HCl and extracted with ethyl acetate. The organic extracts were washed with water, dried, treated with activated carbon and concentrated to
10 yield 8.43 g (63%) of [4-(4-methoxyphenylmethoxy)-phenyl](trimethylsilylethynyl)methylpropanoic acid intermediate: mp. 98-101°C. An analytical sample of the dicyclohexylammonium salt of this acid was prepared and recrystallized from acetonitrile: mp. 148-149°C.

- 15 A solution of crude trimethylsilylalkyne (8.43 g, 0.02 mol) and potassium fluoride (1.65 g, 0.029 mol) was heated at 50°C for 90 minutes in DMF (50 ml). The reaction mixture was cooled, filtered, and the solid potassium salt was washed with diethyl ether. A
20 suspension of the potassium salt in water (50 ml) was stirred and acidified to pH 2 with 12N HCl, and the product was extracted with ethyl acetate. The organic extracts were washed with water, dried, and concentrated to yield 5.44 g (70%) of β -ethynyl-4-(4-methoxyphenyl-methoxy)benzenepropanoic acid: mp. 154-156°C. This acid
25 was characterized further as the dicyclohexylamine which crystallized from methanol:acetonitrile: mp. 153-156°C.

The reaction of the acid prepared above in a procedure analogous to that used in Example 1 yielded [2-
30 ethynyl-2-[4-(4-methoxyphenylmethoxy)phenyl]ethyl]carbamic acid, 4-methoxyphenylmethyl ester. An analytical sample was prepared by recrystallization from ethylacetate: hexane: mp. 112-114°C.

- 35 Deprotection of the above carbamate by the procedure of Example 1 yielded β -ethynyl-4-hydroxybenzene-

1 ethanamine hydrochloride (53%) which was recrystallized
from methanol:ethyl acetate: mp. 160-163°C. An analytical
sample of this compound was prepared by flash
5 chromatography using 75:2 ethyl acetate:14N ammonium
hydroxide as eluant followed by reconversion to the
hydrochloride and recrystallization from methanol:
acetonitrile: mp. 171-173°C.

EXAMPLE 4

10 β-Ethenylbenzeneethanamine Hydrochloride

A solution (2-ethynyl-2-phenylethyl)carbamic
acid, 4-methoxyphenylmethyl ester (1.55 g, 5 mmol),
prepared as in Example 1, in dichloromethane (50 ml) was
hydrogenated at ambient pressure over Aldrich Lindlar
15 catalyst (palladium on calcium carbonate poisoned with
lead) (230 mg) until conversion to product was complete
(typically 90 minutes) as evidenced by TLC. The mixture
was filtered, the filtrate was concentrated, and the
residue was purified by flash chromatography using 3:1
20 hexane:ethyl acetate as eluant to yield 1.46 g (94%) of
(2-ethenyl-2-phenylethyl)carbamic acid, 4-methoxyphenyl-
methyl ester. An analytical sample of this compound was
prepared by repeated flash chromatography using 4:1
hexane:ethyl acetate as eluant: mp. 53-55°C.

25 Deprotection of the above carbamate by the
procedure described in Example 1 yielded β-ethynylbenzene-
ethanamine hydrochloride (38%), after recrystallization
from ethyl acetate: mp. 113-116°C.

EXAMPLE 5

30 Hydrogenation of [2-ethynyl-2-[3-(4-methoxyphenyl-
methoxy)phenyl]ethyl]carbamic acid, 4-methoxyphenylmethyl
ester as in Example 4 yielded [2-ethenyl-2-[3-(4-methoxy-
phenylmethoxy)phenyl]ethyl]carbamic acid, 4-methoxyphenyl-
35 methyl ester.

1 Deprotection of the above carbamate by the
 procedure described in Example 1 yielded β -ethenyl-3-
 hydroxybenzeneethanamine hydrochloride (29%), after
 recrystallization from methanol:ethyl acetate: mp. 153-
 5 155°C.

EXAMPLE 6

β -Ethenyl-4-Hydroxybenzeneethanamine Hydrochloride

Hydrogenation of [2-ethynyl-2-[4-(4-methoxyphenyl-
 10 methoxy)phenyl]ethyl] carbamic acid, 4-methoxyphenylmethyl
 ester as in Example 4 yielded [2-ethenyl-2-[4-(4-methoxy-
 phenylmethoxy)phenyl]ethyl]carbamic acid, 4-methoxyphenyl-
 methyl ester (65%) which was purified by flash
 chromatography with 3:1 hexane:ethyl acetate as eluant.

15 The above carbamate was deprotected by the
 procedure of Example 1 to yield β -ethenyl-4-hydroxybenzene-
 ethanamine hydrochloride (38%), after recrystallization
 from methanol:ethyl acetate: mp. 168-170°C.

EXAMPLE 7

20 An oral dosage form for administering the
 presently invented compounds is produced by screening,
 mixing, and filling into a hard gelatin capsule the
 ingredients in the proportions shown in Table III, below.

25

Table III

<u>Ingredients</u>	<u>Amounts</u>
β -ethynylbenzeneethanamine hydrochloride	50 mg
magnesium stearate	5 mg
30 lactose	75 mg

EXAMPLE 8

The sucrose, calcium sulfate dihydrate and
 β -ethynylbenzeneethanamine shown in Table IV below, are
 35 mixed and granulated in the proportions shown with a 10%

1 gelatin solution. The wet granules are screened, dried,
mixed with the starch, talc and stearic acid, screened and
compressed into 2 tablets.

5 Table IV

<u>Ingredients</u>	<u>Amounts</u>
β -ethynyl-3-hydroxybenzeneethanamine oxalate	100 mg
calcium sulfate dihydrate	150 mg
sucrose	20 mg
10 starch	10 mg
talc	5 mg
stearic acid	3 mg

EXAMPLE 9

15 β -ethynyl-3-hydroxybenzeneethanamine
hydrochloride, 75 mg, is dispensed in 25 ml of normal
saline to prepare an injectable preparation.

While the preferred embodiments of the invention
are illustrated by the above, it is to be understood that
20 the invention is not limited to the precise instructions
herein disclosed and that the right to all modifications
coming within the scope of the following claims is
reserved.

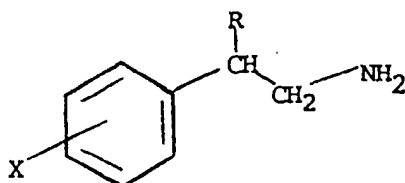
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1 Claims for Contracting States: BE, CH, DE, FR, GB, IT,
LI, LU, NL, and SE

5 1. A compound of the Formula:



in which:

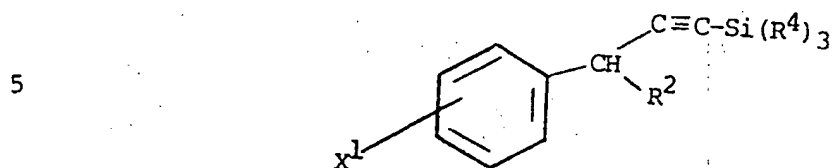
15 X is hydrogen or hydroxy; and
R is ethynyl or ethenyl; or
a pharmaceutically acceptable salt thereof.

20 2. A compound of Claim 1 that is β -ethynylbenzeneethanamine or its hydrochloric acid salt, β -ethynyl-3-hydroxybenzeneethanamine or its oxalic acid salt, β -ethynyl-4-hydroxybenzeneethanamine or its hydrochloric acid salt, β -ethenylbenzeneethanamine or its hydrochloric acid salt, β -ethenyl-3-hydroxybenzeneethanamine or its hydrochloric acid salt, or β -ethenyl-4-hydroxybenzeneethanamine or its hydrochloric acid salt.

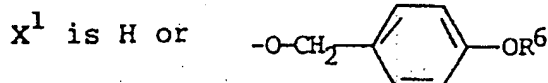
25 3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

30 4. A pharmaceutical composition of Claim 3 wherein the compound is β -ethynylbenzeneethanamine or its hydrochloric acid salt, β -ethynyl-3-hydroxybenzeneethanamine or its oxalic acid salt, β -ethynyl-4-hydroxybenzeneethanamine or its hydrochloric acid salt, β -ethenylbenzeneethanamine or its hydrochloric acid salt, β -ethenyl-3-hydroxybenzeneethanamine or its hydrochloric acid salt, or β -ethenyl-4-hydroxybenzeneethanamine or its hydrochloric acid salt.

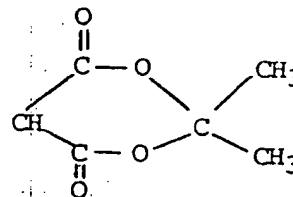
1 3. 5. A compound of the Formula:



10 in which:

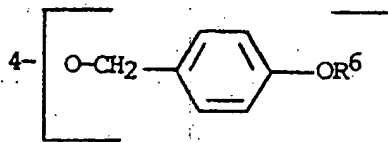


15 R^6 is C_{1-4} alkyl;
 R^2 is $CH(CO_2R^7)_2$; or

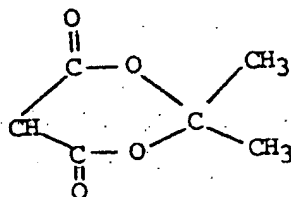


20 R^7 is C_{1-4} alkyl; and
 R^4 is C_{1-4} alkyl

provided that when X^1 is



25 R^2 is



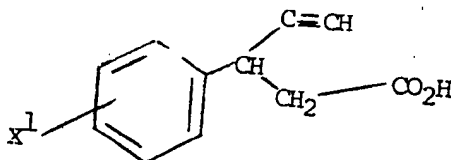
30

6. A compound of Claim 5 that is phenyl
 (trimethylsilylethynyl)methylpropanedioic acid diethyl
 ester, [3-(4-methoxyphenylmethoxy)]-3-(trimethylsilyl-
 ethynyl)methylpropanedioic acid diethyl ester, or 2,2-

35

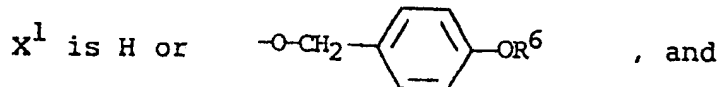
1 dimethyl-5-[4-(4-methoxyphenylmethoxy)phenyl]-
 (trimethylsilylethynylmethyl)-1,3-dioxane-4,6-dione.

7. A compound of the Formula:



10

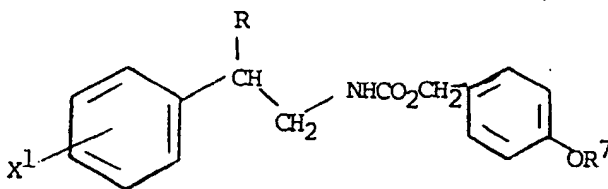
in which:



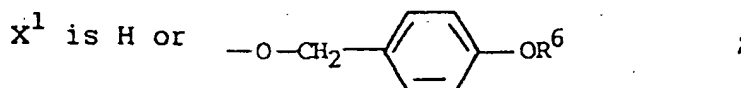
15 R^6 is C_{1-4} alkyl.

8. A compound of Claim 7 that is β -ethynyl-benzenepropanoic acid, β -ethynyl-3-(4-methoxyphenylmethoxy)benzenepropanoic acid, or β -ethynyl-4-(4-methoxyphenylmethoxy)benzenepropanoic acid.

20 9. A compound of the Formula:



in which:



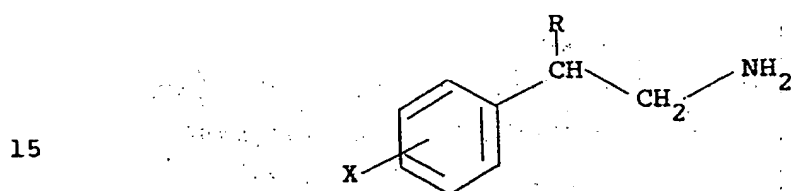
R^6 and R^7 are C_{1-4} alkyl; and

R is $-C \equiv CH$ or $-CH \equiv CH_2$.

10. A compound of Claim 9 that is 2-ethynyl-2-phenylethylcarbamic acid, 4-methoxyphenylmethyl ester,
 35 2-[ethynyl-2-[3-(4-methoxyphenylmethoxy)phenyl]ethyl]-

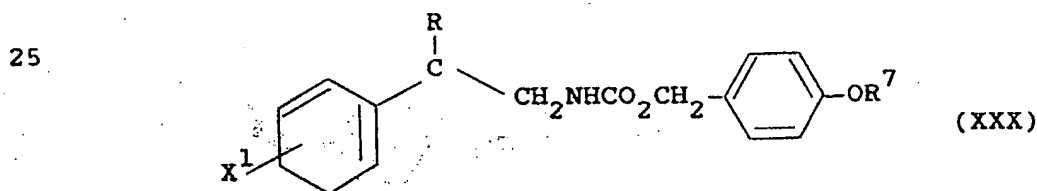
carbamic acid, 4-methoxyphenylmethyl ester, 2-[ethynyl-
2-[4-(4-methoxyphenylmethoxy)phenyl]ethyl]carbamic acid,
4-methoxyphenylmethyl ester, 2-ethenyl-2-phenylethyl-
carbamic acid, 4-methoxyphenylmethyl ester, [2-ethenyl-
5 2-[3-(4-methoxyphenylmethoxy)phenyl]ethyl]carbamic acid,
4-methoxyphenylmethyl ester, or 2-[ethenyl-2-(4-(4-
methoxy phenylmethoxy)phenyl]ethyl]carbamic acid,
4-methoxyphenylmethyl ester.

10 11. A process for preparing a compound of the
formula:




in which

20 X is hydrogen or hydroxy; and
R is ethenyl or ethynyl; or
a pharmaceutically acceptable salt thereof, that comprises
deprotecting a compound of formula (XXX):



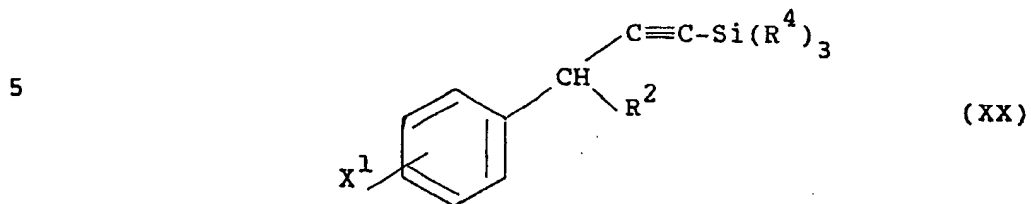
30 in which

R is ethenyl or ethynyl;

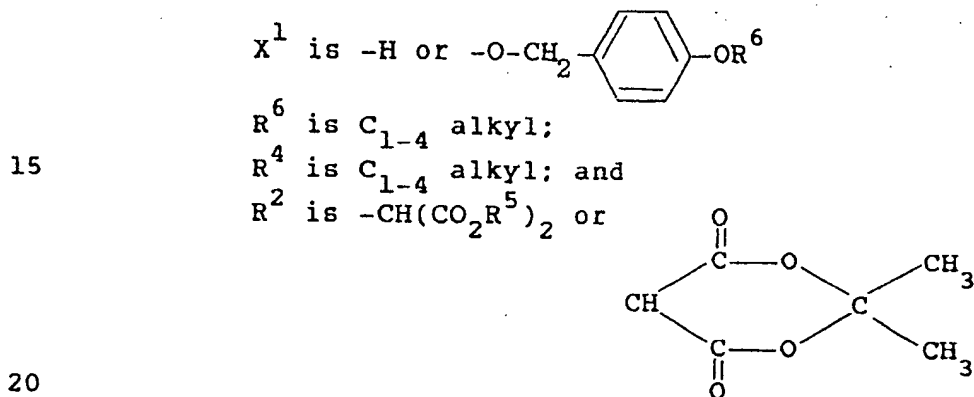
X^1 is H or $-O-CH_2-$  $-OR^6$, and

35 R^6 and R^7 are C_{1-4} alkyl, and optionally thereafter
forming a pharmaceutically acceptable salt.

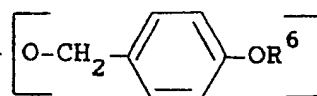
12. A process for preparing compounds of the formula (XX):



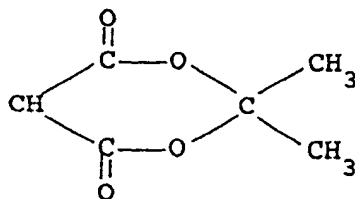
10 in which



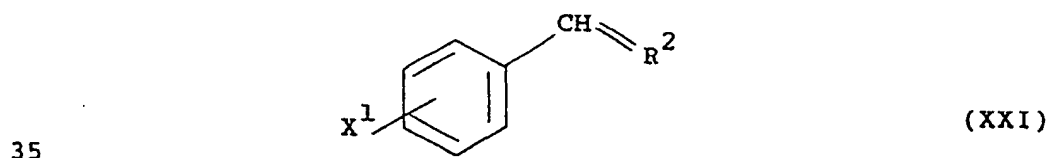
R^5 is C_{1-4} alkyl

provided that when X^1 is 4- 

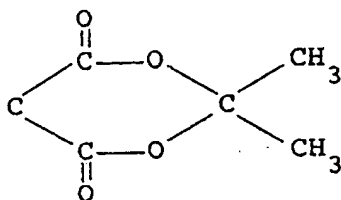
25 R^2 is



30 that comprises reaction of a compound of formula (XXI):



wherein X^1 and R^5 are as in formula (XX) and R^2 is $C(CO_2R^5)_2$ or

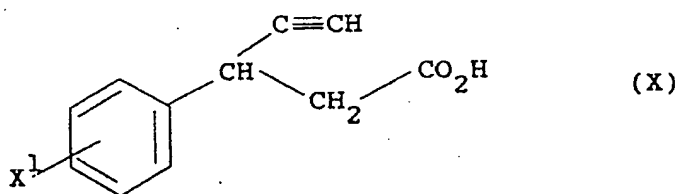


with a compound of formula (XXII)

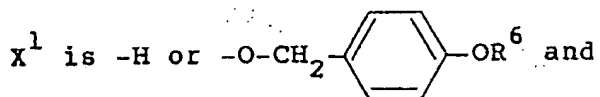


wherein R^4 is as in formula (XX), and Z is Br, Cl, F, or I; followed by addition of the reaction mixture to aqueous acid.

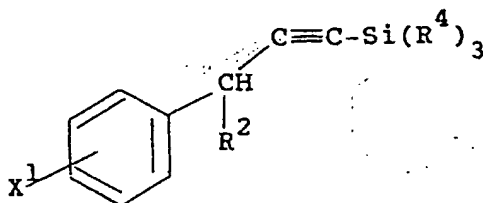
13. A process for preparing compounds of the formula (X):



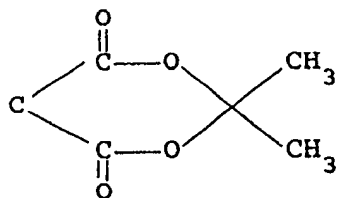
in which



R^6 is C_{1-4} alkyl, that comprises reaction of a compound of the formula:



in which X^1 and R^2 are as described in claim 12. R^4 is C_{1-4} alkyl with a suitable base followed by (a) where R^2 is $CH(CO_2R^5)_2$ acidification with a strong acid and heating the reaction mixture at about 80-120°C in the presence of an aqueous organic base, or (b) where R^2 is



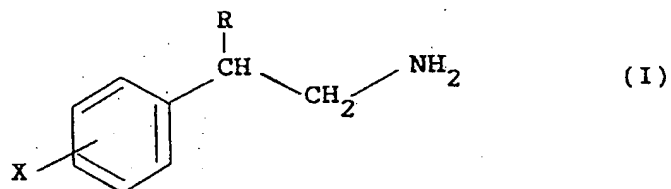
heating at about 40-60°C in a dipolar, aprotic solvent and an organic extract of the reaction mixture with potassium fluoride followed by acidification by addition of a strong acid.

14. A compound of claim 1 for use as a therapeutic agent.

15. A compound of claim 1 for use in the treatment of hypertension.

Claims for Contracting States : AT, GR and ES

1. A process for preparing a compound of the formula:

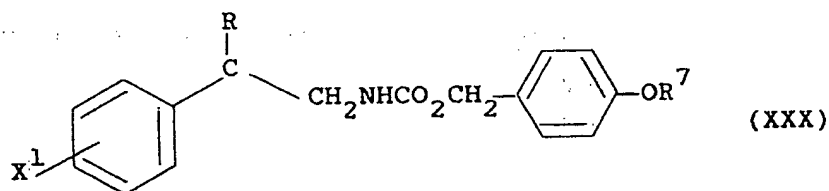


10 in which

X is hydrogen or hydroxy; and

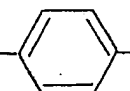
R is ethenyl or ethynyl; or

15 a pharmaceutically acceptable salt thereof, that comprises deprotecting a compound of formula (XXX):



25 in which

R is ethenyl or ethynyl;

X^1 is H or $-O-CH_2-$ , and

30 R^6 and R^7 are C_{1-4} alkyl, and optionally thereafter forming a pharmaceutically acceptable salt.

- 31 -

2. A process according to claim 1 wherein the compound prepared is

β -ethynylbenzeneethanamine or its hydrochloric acid salt;

β -ethynyl-3-hydroxybenzeneethanamine or its oxalic acid

5 salt;

β -ethynyl-4-hydroxybenzeneethanamine or its hydrochloric

acid salt;

β -ethenylbenzeneethanamine or its hydrochloric acid salt;

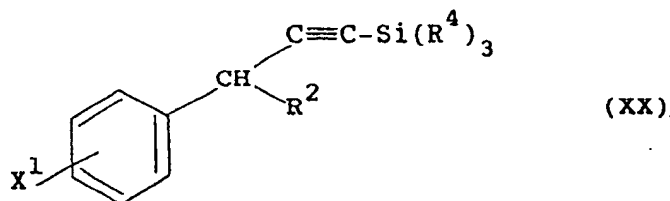
β -ethenyl-3-hydroxybenzeneethanamine or its hydrochloric

10 acid salt, or

β -ethynyl-4-hydroxybenzeneethanamine or its hydrochloric

acid salt.

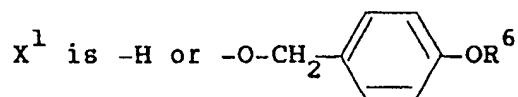
3. A process for preparing compounds of the
15 formula (XX):



20

in which

25

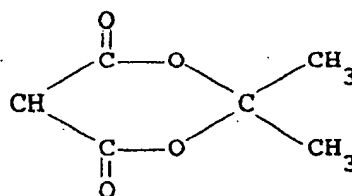


R^6 is C_{1-4} alkyl;

R^4 is C_{1-4} alkyl; and

30


R^2 is $-\text{CH}(\text{CO}_2\text{R}^5)_2$ or

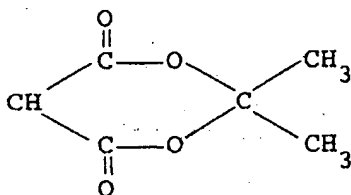


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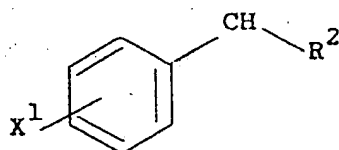
R^5 is C_{1-4} alkyl

- 32 -

provided that when X^1 is 4-

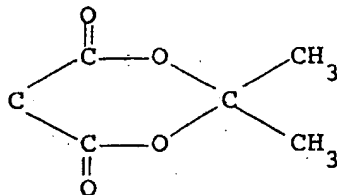
 R^2 is

that comprises reaction of a compound of formula (XXI):



(XXI)

15 wherein X^1 and R^5 are as in formula (XX) and R^2 is $C(CO_2R^5)_2$ or O

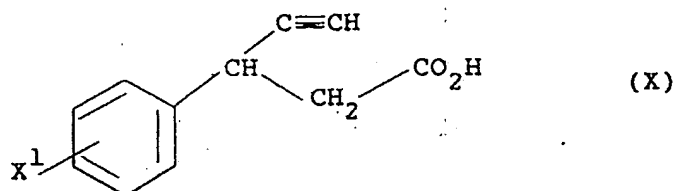


with a compound of formula (XXII)

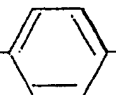


25 wherein R⁴ is as in formula (XX), and Z is Br, Cl, F, or I; followed by addition of the reaction mixture to aqueous acid.

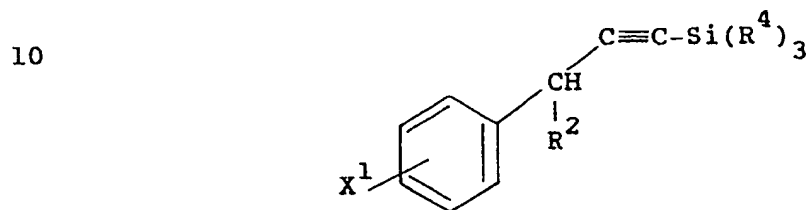
4. A process for preparing compounds of the
30 formula (X):



in which

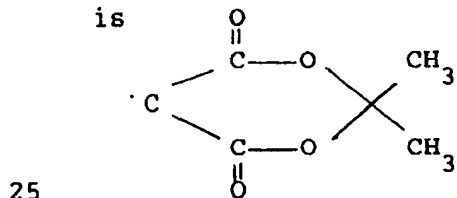
5 X^1 is $-H$ or $-O-CH_2-$  and

R^6 is C_{1-4} alkyl. that comprises reaction of
a compound of the formula:



15

in which X^1 and R^2 are as described in claim 12, R^4
is C_{1-4} alkyl with a suitable base followed by (a) where
 R^2 is $CH(CO_2R^5)_2$ acidification with a strong acid
and heating the reaction mixture at about 80-120°C in the
20 presence of an aqueous organic base, or (b) where R^2
is



heating at about 40-60°C in dipolar, aprotic solvent and
organic extract of the reaction mixture with potassium
fluoride followed by acidification by addition of a
30 strong acid.

5. A process for the preparation of a
pharmaceutical composition which comprises contacting a
compound of structure (I) as described in claim 1 and a
35 pharmaceutically acceptable carrier.

6. A process according to claim 5 in which the compound of structure (I) is
- 5 β -ethynylbenzeneethanamine or its hydrochloric acid salt;
 β -ethynyl-3-hydroxybenzeneethanamine or its oxalic acid salt;
 β -ethynyl-4-hydroxybenzeneethanamine or its hydrochloric acid salt;
 β -ethenylbenzeneethanamine or its hydrochloric acid salt,
10 β -ethenyl-3-hydroxybenzeneethanamine or its hydrochloric acid salt, or
 β -ethynyl-4-hydroxybenzeneethanamine or its hydrochloric acid salt.



European Patent
Office

EUROPEAN SEARCH REPORT

0250264

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 87305476.1
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP - A2 - O 145 361 (MCNEILAB) * Claims 1,10,11; page 6, line 13 - page 9, line 13 *	1,3,7, 9,14, 15	C 07 C 87/29 C 07 C 93/14 C 07 C 85/20 C 07 C 57/42 C 07 C 59/66 C 07 C 51/00
D,A	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 107, July 1963, New York B.M.BLOOM "Some structural considerations regarding compounds that influence monoamine metabolism" pages 878-890 * Page 878, line 1 - page 879, line 20; page 885, line 30 - page 889, line 3 *	1,14	C 07 F 7/08 C 07 C 125/065 A 61 K 31/135
A	EP - A1 - O 011 608 (ASTRA LÄKEMEDEL AKTIEBOLAG) * Claims 1-3; abstract *	1,3,14	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 C 87/00 C 07 C 93/00 C 07 C 85/00 C 07 C 57/00 C 07 C 59/00 C 07 F 7/00 C 07 C 125/00
A	CHEMICAL ABSTRACTS, vol. 65, no. 2, July 18, 1966, Columbus, Ohio, USA BURGER et al. "1-Ethynylphenethylamine" column 3772, abstract-no. 3 772c & J.Med.Chem. 9(4), 469-70(1966)	1,14	
A	US - A - 4 537 974 (LAU) * Formula sheet *	5,12, 13	
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 07-09-1987	Examiner KÖRBER
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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